Cefepime versus extended spectrum β-lactamase-producing *Enterobacteriaceae*

ABSTRACT

The objective of this study was to evaluate the susceptibility to cefepime of a large group of ESBL- producing enterobacteria recently isolated in a Brazilian teaching hospital . The study included 280 strains of ESBL-producing enterobacteria, isolated between 2005 and 2008. The presence of the genes bla_{CTX-M}, bla_{TEM} and bla_{SHV} was determined by PCR and confirmed by nucleotide sequencing. Susceptibility testing for cefepime was performed by disc-diffusion, agar dilution method and E-test®. Among the isolates, 34 (12.1%) presented a cefepime inhibition zone ≥ 21 and MIC ≤ 8 mg/L by agar dilution and E-strip methods. The use of cefepime for the treatment of infections caused by ESBL-producing bacteria has been controversial. Some studies of PD/PK show the probability of achieving the required PD parameters for cefepime, when the MICs were < 8 mg/L, whereas others have reported therapeutic failure with the same MIC. Additional data is essential to come to terms about the report and treatment with cefepime in ESBL-producing organisms especially when these microorganisms are isolated from sterile sites and from critically ill patients.

Keywords: enterobacteriaceae; beta-lactamases; cephalosporin resistance.

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The Clinical Laboratory Standards Institute (CLSI) has recommended, in the period of 2005 to 2009, to perform additional tests for the detection of extended-spectrum beta-lactamases (ESBL) production among *Escherichia coli*, *Klebsiella* spp. and *Proteus mirabilis* isolates. Strains screened as ESBL-producers were reported as resistant to all penicillins, cephalosporins, and monobactams, regardless of the susceptibility test results. The extra step required to perform these tests and the increasing prevalence of ESBL among other *Enterobacteriaceae* have lead specialists to find an alternative to prevent misuse of cephalosporins. Moreover, clinical studies have demonstrated that the success of cephalosporin therapy is more related to the minimum inhibitory concentration (MIC) than to the presence of mechanisms of resistance such as the ESBL production. Based on this knowledge the European Committee on Antimicrobial Susceptibility Testing (EUCAST) and CLSI recommendations have been changed.[1,2] In the CLSI guideline M100-S20 (2010), new susceptibility breakpoints were proposed for ceftriaxone (≤ 1 μg/mL), cefotaxime (≤ 1 μg/mL), ceftazidime (≤ 4 μ g/mL) and aztreonam (≤ 4 mg/L), but not for cefepime (≤ 8 μg/mL).[1] According to this document, the performance of additional tests for ESBL detection would be no longer necessary except for epidemiological or infection control purposes.[1,2]

Cefepime, a fourth-generation cephalosporin, has been introduced into clinical practice in the mid 1990's.[3] It has been recommended for treatment of *Enterobacteriaceae* infections as it has rapid penetration through the outer cell membrane and is stable against AmpC enzymes. Cefepime also demonstrates "*in vitro*" activity against ESBL-producing *Enterobacteriaceae*. In addition, the inoculum effect has not been correlated to cefepime MICs in animal models of ESBL infections.[4] Studies in animal models suggest that the cephalosporin pharmacokinetic and pharmacodynamic (pK/pD) target is similar for the treatment of ESBL- or non-ESBL-producing pathogens (50% T > MIC). Other parameters such as AUC/MIC > 1,654 and C_{min}/MIC > 7.6 also indicated good correlation with clinical cure and bacteriological eradication. According to these studies,

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cefepime current therapeutic dosages would be sufficient to reach the PK/PD target. In this manner, it was not necessary to reduce cefepime susceptibility breakpoints.[5]

The prescription of cefepime for the treatment of ESBL infections imposes a serious clinical dilemma. On one hand, clinical use of cefepime probably would reduce carbapenem consumption. However, treatment failure with cefepime has been reported, especially, in nosocomial pneumonia due to ESBL-producing *Enterobacteriaceae* even in those with MICs ≤ 8 mg/L.[3] In addition, some pK/pD studies show that the probability of achieving the pK/pD target with cefepime is lower when the pathogen MICs varied from 1 to 8 mg/L. In these cases, to achieve the desired pK/pD target, cefepime should be prescribed in prolonged or continuous infusion regimens.[5]

The main objective of our study was to evaluate cefepime susceptibility in a large group of ESBL-producing *Enterobacteriaceae* recently isolated at a Brazilian teaching hospital.

Clinical isolates of ESBL-producing *Enterobacteriaceae* (n = 280) collected from distinct body sites of patients at the Hospital of the *Universidade Federal do Paraná* (HC/UFPR, Curitiba, Southern Brazil) were studied. Only a single representative of a pulsed field gel electrophoresis (PFGE) pattern was included. Species identification was carried out using the VITEK system (bioMérieux, Hazelwood, MO). Susceptibility to cefepime was determined by disc-diffusion, agar dilution method and E-test® according to CLSI guidelines[6] and manufacturer´s instructions (BioMerieux, Hazelwood, MO), respectively. ESBL encoded genes, bla_{CTX-M}, bla_{TEM} or bla_{SHV} were analysed by polymerase chain reaction (PCR) and DNA sequencing.[7]

The cumulative frequency distribution of cefepime is shown in Table 1. Among 280 strains of *Enterobacteriaceae*, 34 (12.1%) isolates showed cefepime inhibition zones ≥ 21 mm or MICs ≤ 8 μg/mL by disc-diffusion and agar dilution/E-test methods, respectively, and would be classified as susceptible to cefepime. They were isolated from blood (8), cerebrospinal fluid (2), peritoneal fluids (3) and urine (21) of patients hospitalized at intensive care units (12), surgical wards (9) and other clinics (13). *K. pneumoniae* (64.7%) and *E. cloacae* (20.6%) were the most frequent species susceptible to cefepime. Regarding the ESBL genes encoded by the *Enterobacteriaceae* isolates, $bla_{CTX-M-2}$ and bla_{SHV-12} were the most frequently detected among isolates susceptible to cefepime as depicted in Figure 1.

Some studies have previously shown that extended-spectrum beta-lactamases are prevalent in many countries around the world, chiefly in South America. Using previous CLSI guidelines, all those isolates would have been considered cefepime-resistant. This recommendation leads to increased use of carbapenems and limited the use of cefepime in ESBL infections. Our study shows that 12.1% of the ESBL-producing *Enterobacteriaceae* tested were susceptible to cefepime. This phenotype was found most frequently in SHV-12-producing *K. pneumoniae*; however, a significant number of CTX-M-producing isolates, which are

Figure 1: Cefepime susceptible species and groups of ESBL.

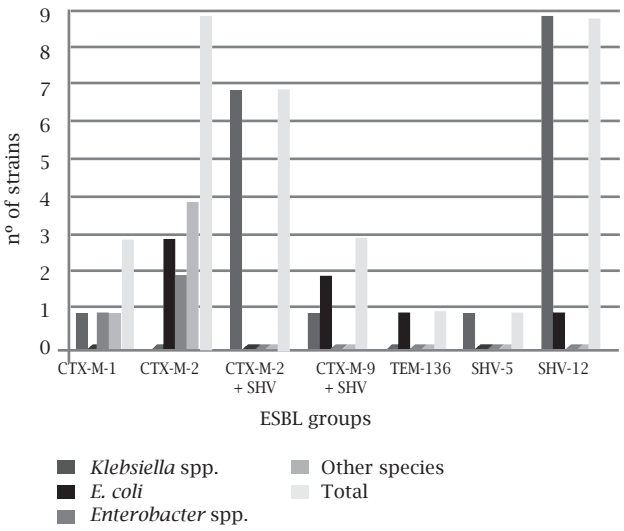

Table 1. Minimal Inhibitry concentration of cefepime in ESBL-producing enterobacteria

Microorganisms	Percentage of isolates inhibited at cefepime MIC (mg/L)											
	0.06[a]	0.12[b]	0.25[c]	0.5[d]	1.0[e]	2.0[f]	4.0[g]	8.0[h]	16.0	32.0	64.0	> 64.0
E. coli	-	-	4.0	4.0	8.0	8.0	8.0	12.0	36.0	72.0	92.0	100
Klebsiella spp.	-	0.8	1.6	1.6	4.9	9.8	13.0	14.6	33.3	53.7	74.0	100
Enterobacter spp.	1.1	1.1	2.2	2.2	3.3	4.4	6.7	7.8	32.2	42.2	54.4	100
Others species	-	4.8	4.8	7.1	9.5	11.9	14.3	14.3	45.2	66.7	71.4	100
Total	0.36	1.43	2.50	2.86	5.36	8.21	10.71	12.14	35.0	53.57	68.93	100

cf, cumulative frequency; MIC, minimal inhibitory concentration; --- signs the susceptible breakpoint. Letters a – h represents the type of genes found, 1 $bla_{CTX-M-2}$; b, 1 $bla_{CTX-M-1}$; 2 $bla_{CTX-M-2}$; c, 3 $bla_{CTX-M-2}$; d, 1bla_{SHV-12}; e, 3 $bla_{CTX-M-1}$; 1 $bla_{CTX-M-2}$; 1bla_{shv-12}; 2$bla_{CTX-M-2}$ +bla_{SHV-12}; f, 1 $bla_{CTX-M-2}$; 3 $bla_{SHV-121}$ $bla_{CTX-M-9}$ +bla_{SHV-5}; 3 $bla_{CTX-M-2}$ + $bla_{SHV-%;}$ g, 2 $bla_{CTX-M-2}$; 1 $bla_{CTX-M-9}$; 1 $bla_{tem-136}$; 3 bla_{SHV-12} ;h, 2 $bla_{CTX-M-2}$; 1 bla_{SHV-5}; 1 $bla_{CTX-M-2}$ +bla_{SHV-5}.

the most prevalent in South America, was also susceptible to cefepime. In other geographic regions, where group TEM or SHV is prevalent, the cefepime susceptibility among ESBL-producing isolates might be even higher. In North America, 93.8% and 92.0% of the ESBL-producing *E. coli* and -*K. pneumoniae*, respectively, were susceptible to cefepime.[8] In Taiwan, Liao *et al*. reported that 77% and 73.4% of the ESBL-producing *E. coli* and *K. pneumoniae* were cefepime susceptible.[9]

In this study, 4.8% of ESBL-producing enterobacteria isolates have shown MIC ≤ 1 mg/L. PK/PD studies suggest that successful outcome using conventional regimens of cefepime (50% T > MIC) could be achieved for treatment of infections caused by such isolates, regardless ESBL production.[5] Most authors would consider acceptable the clinical use of cefepime in these conditions. However, clinical outcomes are contradictory for infections caused by isolates, in which MICs varied from 1 to 8 mg/L. For infections caused by such isolates, pK/pD studies have demonstrated that the pharmacodynamic target could be achieved only if the infusion time or dosage were modified.[4] In this manner, EUCAST recommends that only isolates exhibiting MICs for cephalosporins, including cefepime, ≤ 1 mg/L must be reported as susceptible to cephalosporins, regardless of ESBL production.[2]

Several reports have shown therapeutic failure when the patient had received cefepime for treatment of non-urinary infections caused by ESBL-producing organisms. These data indicate that the body site of infection might affect cefepime effectiveness.[11] In our study, although most of the ESBL-producing isolates susceptible to cefepime were from urinary tract infections, 38.2% of these isolates were originated from sterile body sites of infection and 35% were from critically ill patients, increasing the chance of a possible therapeutic failure. In addition, the safety of using cefepime has been questioned. A meta-analysis study associated the use of cefepime with increase in the mortality rates.[12] Although this finding has been questioned by some authors, other studies have reported many untoward effects of this drug.[3] Therefore, the prescription of modified cefepime regimens especially those using higher doses need more extensive evaluation before their use is encouraged.

At this moment, it would be difficult to consider cefepime a safe option for treating ESBL infections, particularly those caused by isolates with MICs between 1 and 8 mg/L or cultured from sterile sites and/or from critically ill patients. Moreover, the discordance between CLSI and EUCAST guidelines may cause confusion among microbiologists and infectious diseases specialists. While the role of cefepime in the treatment of ESBL infections is not established by clinical studies, compliance with the European guidelines seems more appropriate.

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